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Abstract: Application of gymnemic acid (GA) on the tongue depresses the taste of sucrose in man. This effect, as indicated by electrophysiological responses, has been found to be absent in three nonhuman primate species. In the present behavioral study the effect of GA on taste responses in 22 primate species, with two subspecies, and 12 human subjects has been investigated. In all the nonhuman primates studied, including the Pongidae which are closely related to man, GA did not suppress the response to sucrose, only in man did GA have a depressing effect

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Effects of gymnemic acid on sweet taste perception in primates

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Abstract. Application of gymnemic acid (GA) on the tongue depresses the taste of sucrose in man. This effect, as indicated by electrophysiological responses, has been found to be absent in three non-human primate species. In the present behavioral study the effect of GA on taste responses in 22 primate species, with two subspecies, and 12 human subjects has been investigated. In all the non-human primates studied, including the Pongidae which are closely related to man, GA did not suppress the response to sucrose, only in man did GA have a depressing effect.

Introduction

In 1847, in a communication to the Linnean Society of London, mention was made for the first time of a particular property of a plant native to India belonging to the Asclepiadaceae: 'A further communication, from a letter written by Mr Edgeworth, dated Banda, 30th August, 1847, was made to the meeting, reporting a remarkable effect produced by the leaves of *Gymnema sylvestris R.Br.* upon the sense of taste, in reference to diminishing the perception of saccharin flavours'. Further details relating to the effect of these leaves were given by Falconer (1847/48).

Hooper (1887a,b) tried to isolate the active principle from the leaves of *G. sylvestre*, and found it to be composed of an organic acid and a glycoside; he called it gymnemic acid (GA). After Hooper (1889), Kiesow (1894), Power and Tutin (1904), Posternak and Schopfer (1950), Da Pieda de Noronha and Veloso Pinto (1954), Khastgir *et al.* (1958) had all tried in vain to prepare a pure sample of GA, Warren and Pfaffmann (1959) were the first to obtain a relatively pure sample of GA ($C_{32}H_{55}O_{12}$, mol. wt. 631.4). By using a modified method, Yackzan (1966) obtained similar microcrystals from the leaves as those found by Warren and Pfaffmann. In the following year Stoecklin *et al.* (1967) and Stoecklin (1967) reported that GA is a mixture of triterpene saponins (GA A1-A4). Sinsheimer *et al.* (1968, 1970), Sinsheimer and Rao (1970) as well as Kurihara (1969) contributed to the elucidation of the structure of GA; a review on the chemistry of GA was given by Kurihara (1971), and Dateo and Long (1973) carried out studies on the isolation and heterogeneity of GA A1. According to Kurihara (1969), GA A1 shows the highest anti-sweet activity.

The psychophysical effects of GA in man have also been investigated. After the depressing effect had first been observed by the natives of India and subsequently confirmed by Edgeworth (1847) himself, it was confirmed by Hooper (1887a,b),

Shore (1892), Kiesow (1894), Goy (1896), Mhaskar and Caius (1930), Warren and Pfaffmann (1959), Diamant *et al.* (1965), Borg *et al.* (1967), Warren *et al.* (1969), Bartoshuk *et al.* (1969), Kurihara *et al.* (1969), Meiselman and Halpern (1970), Bujas and Pfaffmann (1971), Diamant *et al.* (1972) and finally DeSimone *et al.* (1980). Very recently Chakravanti and Debnath (1981) found that in GA A1 the sugar moiety is glucuronic acid alone, while in GA A2 and GA A3, it is glucuronic acid and galactose.

The literature mentioned above is anything but unanimous regarding the duration of the effect of GA. Edgeworth (1847) states that the depressing effect after chewing the gymnema leaves continues for a period of 24 h, but according to Hooper (1887a,b) 'the effect peculiar to the leaf does not last twenty-four hours, as stated, but for only one or two hours'. Also, the views on the effect of GA on the other three taste qualities differ: Hooper (1887a,b) described a limited effect of the gymnema leaves on sweet and bitter, whereas Shore (1892) observed a slight effect on the bitter and also on the salty taste. Kiesow (1894) reports: 'thus gymnemic acid influences all the four taste qualities, although the effect on salt and sour is hard to evaluate'. Also Goy (1896) finds, in addition to the effect on the sweet taste, a somewhat lesser effect on bitter tasting substances. Bartoshuk *et al.* (1969, 1974) suggested on the other hand that the apparent reduction in non-sweet qualities might have resulted from simple cross-adaptation since the early workers did not rinse GA off the tongue carefully.

Although the depressing effect of GA on the sweet taste in man was consistently confirmed, it was not until 1965 that Snell tested GA for the first time in a non-human primate by electrophysiological means; he studied the squirrel monkey (*Saimiri sciureus*), which is indigenous to S. and Central America. Diamant *et al.* (1972) carried out similar studies on the African *Cercopithecus aethiops* and Hellekant *et al.* (1974) investigated the same primate and also the Asian *Macaca fascicularis*. These three electrophysiological studies, in which GA did not appear to affect non-human primates, do not allow general conclusions to be drawn as there are ~185 primate species which show considerable differences. Thus, the purpose of the present work was to study by behavioral means further non-human primates, particularly the Hylobatidae and Pongidae, as phylogenetically these are closest to man.

Methods

The behavioral studies were made with seven primate species and one of them with two subspecies in the Zoological Garden of Zürich and with 15 primate species, one of them with two subspecies, in the Anthropological Institute of Zürich University (see Table I). The 110 individuals studied include representatives from all infra-orders of the primates without the Tupaiiformes and Tarsiiformes but include 12 individuals of *Homo sapiens* for checking the effect of GA from time to time.

The smaller-sized primates had two bottles, one with tap water and one with a solution of sucrose in tap water, attached to the side of their cages (*cf.*, Glaser, 1968), the medium-sized primates were provided inside their cages with two larger drinking bowls which they could not knock over, and the big anthropoids were

Table 1. Intake of water and sucrose before and after GA treatment in various numbers of primate species investigated by means of behavioral tests

Familia	Genus		Mean intake (ml)**					
			before GA				after GA	
			1st day		2nd day		2nd day	
		n	water	sucrose	water	sucrose	water	sucrose
Lemuridae	*Lemur catta*	12	10	138	10	70	8	60
	Lemur mongoz	3	0	33	4	28	3	54
	Cheirogaleus medius	1	0	18	0	11	1	19
Lorisidae	*Loris tardigradus*	3	3	13	2	15	6	18
Callitrichidae	*Callithrix jacchus jacchus*	12	2	53	3	51	3	55
	Callithrix jacchus penicillata	3	5	67	3	63	4	75
	Cebuella pygmaea	3	4	14	4	31	4	29
	Saguinus midas niger	12	2	36	2	44	2	38
	Saguinus fuscicollis nigrifrons	2	4	50	3	50	4	50
	Saguinus oedipus oedipus	7	2	23	1	39	2	39
Cebidae	*Aotus trivirgatus*	7	12	61	3	52	7	67
	Saimiri sciureus	1*	0	14	0	26	0	49
Cercopithecidae	*Macaca fascicularis*	*						
	Macaca mulatta	2	0	50	0	50	0	50
	Macaca nigra	7	–	+	–	+	–	+
	Cercocebus atys	1	0	50	0	50	0	50
	Cercopithecus aethiops	1*	0	50	0	50	0	50
	Cercopithecus pygerythrus	2	2	50	0	50	2	50
	Cercopithecus nictitans stampflii	1	0	50	0	50	0	50
Hylobatidae	*Hylobates pileatus*	2	–	+	–	+	–	+
	Symphalangus syndactylus	4	25	250	3	250	4	250
Pongidae	*Pongo pygmaeus pygmaeus*	2	–	+	–	+	–	+
	Pongo pygmaeus abelii	5	–	+	–	+	–	+
	Pan troglodytes troglodytes	4	–	+	–	+	–	+
	Gorilla gorilla gorilla	2	–	+	–	+	–	+
Hominidae	*Homo sapiens*	12		sweet		sweet		not sweet

*Also investigated electrophysiologically: *S. sciureus* (n = 1), *M. fascicularis* (n = 2), *C. aethiops* (n = 8). (See text for authors.)

**Consumptions – and + are determined only by observation: – = practically no intake; + = intake before and after GA equal.

tested with the aid of their usual drinking mugs. All the animals were at all times able to choose between two liquids.

Before the primates were confronted with GA A1 they were first trained to sample a 0.1 mol/l sucrose solution in a two-bottle preference test; the smaller-sized Callitrichidae and Prosimae of the institute were trained to sample a 0.2 mol/l sucrose solution, because they are less sensitive to sucrose (Glaser, 1980). We then recorded the consumption of the sucrose solution *versus* water in two sessions (maximal duration of one session 120 min). Before the third session two slices of a banana or potato soaked in a fresh GA solution (50 mg in 50 ml of a 0.01 mol/l $NaHCO_3$ solution) were applied to the tongue for ~3 min. Immedi-

ately afterwards, the animals can start to drink. The consumption of the sucrose solution *versus* water before and after application of GA shows the taste modifying effect of this substance, if any.

GA was tested by humans (*H. sapiens*) as described by Kurihara (1969) and also with the slices of banana as described above.

Results

For none of the 19 individual prosimians given in Table I (*Lemur catta, Lemur mongoz, Cheirogaleus medius* or *Loris tardigradus*), could a depressing effect on the sucrose taste be observed. The animals drank within 2 h after administration of GA the same volume of sucrose solution as they did on the preceding days on which no GA was given. Also, the 47 individual S. and Central American platyrrhines Callitrichidae and Cebidae have so far shown no depressing effect.

The absence of a perceptible change in the drinking behavior of the 14 individual catarrhines (Cercopithecidae from Asia and Africa) confirms the electrophysiological results of Snell (1965), Diamant *et al.* (1972) and Hellekant *et al.* (1974) given in the Introduction and Table I.

The reaction to GA of the Hylobatidae and Pongidae, which are most closely related to man from a phylogenetic point of view, can best be demonstrated by the experiment with *Symphalangus syndactylus*. Two animals of this species drank 250 ml of 0.1 mol/l sucrose solution and 25 ml water within 4 min on the first day. On the second day, they drank within 3 min the same amount of sucrose solution and only 3 ml water. On the third day the two animals were given the banana slices which had been soaked in the GA solution after which they drank 250 ml of the sucrose solution and 4 ml water, again within 3 min. The amount of sucrose solution was consumed in the same short time before and after GA, which indicates that there was no change in sweetness impression. This result clearly shows that GA had no influence on the sucrose intake of these two Symphalangus animals. Similarly clear results were also obtained for *Hylobates pileatus* and all the Pongidae tested.

In summary, it can be said that because GA was found to have no depressing effect on the taste of sucrose in the prosimians, platyrrhines and catarrhines nor in the Hylobatidae and Pongidae, the effect of GA among the primates is apparently only found in *H. sapiens*. Obviously the GA effect is a distinct feature of taste physiology which constitutes a clear dichotomy between non-human primates and *H. sapiens*.

Discussion

Several authors reported the gustatory effects of GA in procaryotes and invertebrates. As early as 1974, Hazelbauer showed that GA does not inhibit the chemotactic response of the bacterium *Escherichia coli* to carbohydrates. Larimer and Oakley (1968) reported that GA is totally ineffective in blocking the sugar response in the crayfish *Procambarus clarkii*. The same authors found in behavioral tests as well as in electrophysiological recordings from chemoreception hairs of flesh flies *Sarcophaga spp.* of the Sarcophagidae family, that gymnema extract produced no measurable inhibition of sugar chemoreception. In

Table II. Gustatory effects of gymnemic acid in procaryotes, invertebrates and mammals

Ordo	Familia	Genus	Effect*
Eubacteriales	Bacteriaceae	*Escherichia coli*	–
Decapoda	Astacidae	*Procambarus clarkii*	–
Lepidoptera	Noctuidae	*Prodenia eridania*	–
	Lasiocampidae	*Malacosoma sexta*	–
	Pieridae	*Pieris brassicae*	–
Diptera	Muscidae	*Musca domestica*	+
	Calliphoridae	*Lucilia caesar*	+
	Sarcophagidae	*Blaesoxipha cessator*	+
		Sarcophaga spp.	–
Lagomorpha	Leporidae	*Oryctolagus cuniculus*	–
Rodentia	Muridae	*Rattus norvegicus*	–
		Cricetus cricetus	+
		Mesocricetus auratus	+
Carnivora	Canidae	*Canis familiaris*	+
Artiodactyla	Suidae	*Sus scrofa*	–

*Effect (+) or no effect (–) of gymnemic acid; authors are mentioned in the text.

contrast Kennedy *et al.* (1975) found that in other fly species, *viz. Blaesoxipha cessator* (also of the Sarcophagidae family), *Musca domestica* and *Lucilia caesar*, GA blocks the sucrose response as well as the NaCl response; from neurophysiological observations they concluded that this can be a narcotic effect. Granich *et al.* (1974) found that application of GA did not act in the larvae of the noctuid moth, *Prodenia eridania* (Southern army worm), as it did in mammals (*viz.* suppressing the sweetness of sugars). Schoonhoven (1974) found that the sugar receptors of *Pieris brassicae* and *Manduca sexta* larvae keep firing when stimulated with sucrose during or after exposure of the receptors to GA for periods of up to 5 min.

Tests in mammals, other than primates, showed that GA has no sweetness-depressing effect in the rabbit *Oryctolagus cuniculus*, the pig *Sus scrofa* (Hellekant, 1976) or the rat *Rattus norvegicus* (Lovell *et al.*, 1961; Larimer and Oakley, 1968; Diamant *et al.*, 1972; Hellekant and Gopal, 1976). But in the hamsters *Cricetus cricetus* and *Mesocricetus auratus* (Hagstrom, 1957; Yackzan, 1969; Bartoshuk, 1970; Faull and Halpern, 1971; Hellekant and Gopal, 1976), and the dog *Canis familiaris* (Anderson *et al.*, 1950; Hellekant, 1976), GA suppresses the response to sucrose. In this study, we were unable to demonstrate an effect of GA in the non-human primates (see Table I). In the primates, *C. aethiops* and *M. fascicularis*, which we previously tested electrophysiologically (Hellekant *et al.*, 1974), we have not been able to demonstrate any effect of GA which is in total agreement with our results obtained with the behavioral technique in this study.

Hellekant (1977) showed that in *Macaca mulatta* there was also no effect of GA on the sucrose sweetness. However, the sweetness-inducing effect of miraculin was diminished. In that study, GA was applied in the same way as we adopted

here. This indicates that on applying GA onto the tongue by means of banana slices all taste receptors were covered.

It is difficult to draw conclusions regarding any phylogenetic relationships from the efficacy of GA, as was done for the effect of thaumatin by Glaser *et al.* (1978). As GA has no effect in procaryotes, but has in some fly species of the invertebrates, and in the vertebrates is only effective in hamster species, dog and man (see Tables I and II), it would require numerous tests with different animal species to obtain a better view of the effect of GA.

In discussing the mode of action of GA, it should be borne in mind that within the above mentioned Sarcophagidae family *Sarcophaga spp.* and *B. cessator* show different responses. This also holds for rats and hamsters within the family of the Muridae. These different reactions of very closely related species to the same substance have been shown repeatedly by Glaser (1979) in the case of primates. In tests with human subjects, it appeared that with some persons the effect of GA was strong and prolonged whereas with others it was less pronounced and short-lived; these variations should be the subject of further investigation.

DeSimone *et al.* (1980) found that GA is a highly surface-active substance and may produce effects on taste reception at the level of the plasma membrane; there is a subtle interplay between surfactant and receptor which could depend on species variations in cell lipoprotein structure. Presumably the different reactions to GA in closely related animal species may be attributed to the different reactions at the plasma membrane. Until these reactions are elucidated, Hellekant and Gopal (1976) may be right in asserting that 'the mechanism of action of GA is not known, and more data are required before possible mechanisms can be discussed'.

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